

Nontuberculous Mycobacteria

II: Nested-Cohort Study of Impact on Cystic Fibrosis Lung Disease

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The prevalence of nontuberculous mycobacteria (NTM) is high (approximately 13%) in sputum of patients with cystic fibrosis (CF), but the impact on lung disease is unknown. We followed 60 incident NTM-positive and 99 culture-negative patients with CF for 15 months and assessed clinical impact of NTM by FEV₁ and high-resolution computed tomography (HRCT) of the chest. *Mycobacterium avium* complex was seen in 75% of NTM-positive subjects. The annual rate of decline in FEV₁ was not different among control versus NTM-positive subjects who did not, or did, meet American Thoracic Society microbiologic criteria for NTM disease (3 ± 1 , 3 ± 2 , and $5 \pm 2\%$, respectively). More subjects with three or more positive cultures for NTM had two or more characteristic findings on entry HRCT (60%, 9/15) as compared with subjects with two positive cultures or less (32%) or negative cultures (19%; $p < 0.02$). All subjects with three or more positive cultures and exit HRCTs ($n = 6$) showed progression of HRCT findings, whereas only 17% of subjects with two positive cultures or less had progression ($p = 0.0006$). In summary, no significant short-term effect on FEV₁ was detected in patients with multiple positive NTM cultures, but an abnormal HRCT was predictive of progression. Patients with CF and multiple positive NTM cultures, characteristic HRCT findings, and progression of HRCT changes should be monitored closely and considered for antimycobacterial therapy.

Keywords: cystic fibrosis; nontuberculous mycobacteria; *Mycobacterium avium*-intracellulare; *Mycobacterium abscessus*; computed tomography of chest

The prevalence of nontuberculous mycobacteria (NTM) in the lower respiratory tract of older subjects with cystic fibrosis (CF) is high (approximately 13%) relative to the background population and to other disease groups. We reported, in a cross-sectional study, an increase in the prevalence of NTM with age and an association with relatively preserved lung

function (1). However, the impact of these organisms on the clinical course of CF lung disease has not been prospectively evaluated.

Criteria for the diagnosis of disease caused by NTM in persons without CF have been published (2). Diagnosis requires the presence of (1) clinical signs and symptoms; (2) multiple positive sputum cultures, recovery of NTM in large amounts on microbiologic smears and cultures of bronchoscopic samples, and/or compatible histopathology with a positive NTM culture; and (3) compatible radiographic findings. Defining NTM disease in patients with CF is particularly challenging, given the considerable overlap of the clinical and radiographic criteria between disease caused by NTM and CF.

Although case reports of an apparent association between NTM and a decline in clinical and radiographic features have been published, other reports of this relationship suggest these organisms may coexist in the lower airways of some subjects with CF without significant adverse effect (3–13). There has been no prospective, rigorous evaluation of the impact of NTM in the lower airways on lung function, and radiographic findings of the presence of NTM in CF have not been published. This study was designed to look systematically at the (short-term) longitudinal effects of NTM on the clinical course of CF lung disease, as assessed by changes in spirometry and chest computed tomography (CT), to develop criteria that may indicate a need for further diagnostic evaluation and/or initiation of specific antimycobacterial therapy.

METHODS

Study Design

A previous multicenter cross-sectional study assessed prevalence of NTM (1) in three sputum samples over a year. The current nested-cohort design identified incident NTM-positive subjects (at least one prior negative culture) from the prevalence study (Figure 1), matched by age, sex, and FEV₁ to two culture-negative “controls” in that study (Figure 1). Subjects were followed for 15 months, and sputum was tested on each visit. Chest radiographs were performed at entry, 6, and 15 months; chest HRCT was performed at entry and 15 months on NTM-positive subjects and 20% of the control subjects.

Subjects

We enrolled from 17 U.S. centers, excluding subjects with *Burkholderia cepacia*. Eleven NTM-negative “control subjects” turned culture-positive, and re-enrolled as NTM-positive subjects; data from these control subjects were excluded. Only one control was available for 10 culture-positive subjects; four controls were transplanted, five died, and two withdrew. The protocol was approved by Institutional Review Boards at participating sites.

Clinical and Laboratory Evaluation

Clinical data were recorded at each visit (14–16). Sputum was processed at site labs (17, 18). Positive cultures were typed and then sent to the

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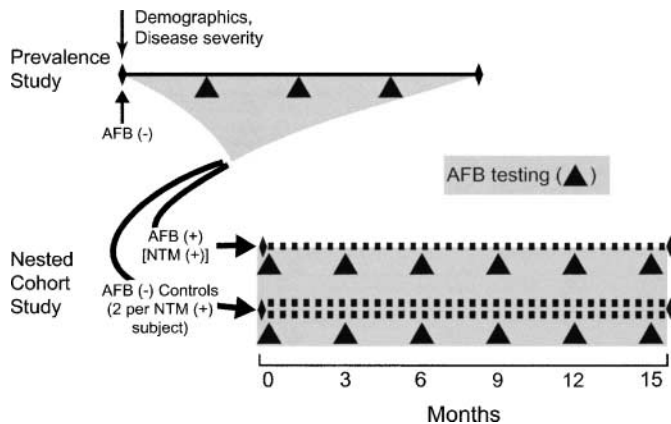


Figure 1. Timeline depicting the relationship between the previous cross-sectional, prevalence study and this current nested-cohort study, which was performed in subjects identified by the prevalence study. Subjects with least one negative acid fast bacillus (AFB) culture in the prevalence study were entered into the current (nested-cohort) study at the time of their first positive AFB culture and were matched to two subjects who were NTM-culture-negative. Both NTM-positive subjects and their matched, culture-negative control subjects were assessed clinically every 3 months for 15 months with specimens for mycobacterial culture obtained at each visit.

reference laboratory (University of Texas Health Center, Tyler, TX) for final identification.

Radiographic Evaluation

Original radiographs (posteroanterior and lateral chest) were scored at Chapel Hill (Birmingham Roentgenogram Score) (19). HRCT scans were performed at respective sites and evaluated in Chapel Hill (P.L.M.) without knowledge of culture status. HRCTs were assessed for four characteristic findings associated with NTM in subjects without CF: (1) cystic and/or cavitary parenchymal lung disease, (2) subsegmental (or larger) parenchymal consolidation, (3) single or multiple pulmonary nodules, and (4) tree-in-bud opacities (20–22).

Statistical Analysis

Descriptive statistics were used to identify differences between NTM-positive and control (NTM-negative) subjects. The χ^2 test was used to compare categorical characteristics at baseline between NTM-positive and control subjects, and two-tailed Student's *t* tests (independent) were used for continuous variables.

NTM-positive subjects were categorized by American Thoracic Society (ATS) microbiologic criteria for disease; subjects with three or more positive cultures, or two positive cultures and a positive smear, “met criteria,” but subjects with two positive cultures or less “did not meet criteria.” Univariate comparisons of control subjects versus the two groups of NTM-positive subjects (“meeting” and “not meeting” criteria) were assessed by analysis of variance for baseline characteristics, days of hemoptysis, corticosteroid and intravenous antibiotic use, and microbiology. Chest radiograph scores were assessed by multivariate analysis of variance (control subjects vs. two groups of NTM-subjects) versus NTM status and time. Differences in baseline and serial HRCT findings were assessed by Fisher's exact test.

We used mixed linear regression models to test whether FEV₁ decline was different between NTM-positive subjects and control subjects and among NTM-positive subjects who did, or did not, meet microbiologic criteria (23). The first model used data collected at the beginning of the previous prevalence study and during this current study, including covariates (age, sex, and body mass index). The second model covered only data from entry into this study (Figure 1), including additional covariates (FEV₁, corticosteroids, and parenteral antibiotics). The effect of NTM status on FEV₁ was tested by comparing two models using log-likelihood statistics. Pairwise differences were assessed between the two categories of NTM-positive subjects and control subjects.

RESULTS

Baseline Characteristics

Sixty NTM-positive and 99 control subjects were enrolled from 17 U.S. CF centers (Table 1). Although NTM-positive subjects tended ($p = 0.16$) to be slightly older (average, 2 years) than control subjects at entry into the cohort study, they also tended to have higher FEV₁ values (approximately 5%, $p = 0.19$) and slightly better Birmingham Composite Radiograph Scores (approximately 1.0; $p = 0.08$). The chest CT findings tended to parallel the pattern seen with FEV₁ values and Birmingham Radiograph Scores. Specifically, more NTM-positive subjects tended to have at least two chest CT findings that are characteristic of NTM disease in subjects without CF as compared with control subjects ($p = 0.11$) (see further comments below). There were no significant differences in sex, body mass index, or the frequency of pancreatic enzyme use.

Mycobacterial Cultures

Control subjects had 7.8 ± 0.1 (range 4–11) cultures, and NTM-positive subjects had 8.9 ± 0.2 (range 5–13) cultures over 16 months. Before the first positive culture, 23 (38%) of NTM-positive subjects had one negative culture, 19 (32%) had two negative, and 18 (30%) had three or more negative cultures.

TABLE 1. COMPARISON OF NONTUBERCULOUS MYCOBACTERIA-POSITIVE SUBJECTS AND NONTUBERCULOUS MYCOBACTERIA-NEGATIVE CONTROL SUBJECTS AT ENTRY INTO THE NESTED-COHORT STUDY

Characteristic	NTM-Positive Subjects (n = 60)	Control Subjects (n = 99)	p Value*
Sex, % male	48	45	0.72
Age at enrollment, yr, mean	28.5 ± 1.4	26.2 ± 0.9	0.16
FEV ₁ , % predicted, mean	57.6 ± 2.9	52.8 ± 2.2	0.19
Body mass index, kg/m ² , mean	20.7 ± 0.4	20.0 ± 0.3	0.18
Use of pancreatic enzymes, %	95	95	0.99
Birmingham Radiograph Score, mean [†]	17.6 ± 0.5	$16.6 \pm 0.3^{\ddagger}$	0.08
Characteristic CT findings, % [§]	40	19	0.11

Definition of abbreviations: CT = computed tomography; NTM = nontuberculous mycobacteria.

* χ^2 for dichotomous variables, and *t* test for continuous variables.

[†] Composite score.

[‡] n = 96.

[§] At least two of the following features: cysts/cavities, consolidation, nodules, tree-in-bud.

^{||} Subjects with entry CT scans: cases, n = 53; control subjects, n = 21.

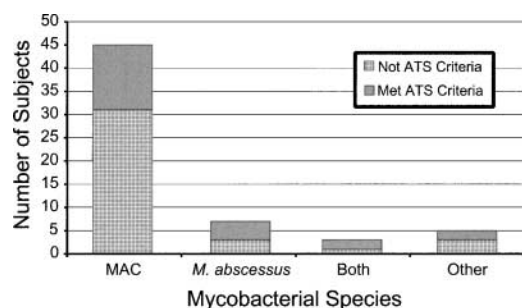


Figure 2. The number of subjects having positive mycobacterial cultures, grouped by mycobacterial species. The bars represent the number of subjects who did not meet the ATS microbiologic criteria for NTM disease (hatched bars, lower stacks) and those subjects who did meet ATS criteria (solid bars, upper stacks).

The majority of NTM-positive subjects had only a single positive culture ($n = 34$, 57%) with only two of these having a positive smear; eight (13%) had two positive cultures, four of whom had positive smears; eight (13%) had three positives with half having positive smears; and 10 (17%) had more than three positive cultures with half having at least one positive smear. Of the 60 NTM-positive subjects, 22 (37%) met the ATS microbiologic criteria for NTM disease.

Mycobacterium avium complex (MAC) was recovered from the majority of the NTM-positive subjects ($n = 45$, 75%) with a third (14) of these meeting ATS criteria (Figure 2). *Mycobacterium abscessus* was recovered from seven subjects (12%), and four of those met ATS microbiologic criteria. Subjects with *M. abscessus* tended to meet ATS NTM criteria more frequently than subjects with MAC or other NTM organisms (odds ratio = 3.2, 95% confidence interval 0.8, 12.9; $p = 0.1$). One subject had three different organisms—*M. abscessus*, *Mycobacterium kansasii*, and *Mycobacterium mageritense*; three subjects had both MAC and *M. abscessus*; one subject had both MAC and *Mycobacterium goodii* (multiple isolates); and one had *Mycobacterium pergrinum*, one had *Mycobacterium lentiflavum*, and one had *M. kansasii* (Figure 2).

Clinical Variables

There was no significant difference in the number of days with hemoptysis among the control subjects and NTM-positive subjects that either did not, or did, meet ATS microbiologic criteria (Figure 3A). Steroids were used less frequently in the NTM-positive subjects who met ATS criteria as compared with the NTM-negative control group ($p < 0.05$). Intravenous antibiotics were used more frequently in the control group compared with the NTM-positive subjects ($p < 0.05$, Figure 3A). There were no significant differences among the three groups in the recovery of *Pseudomonas aeruginosa* or *Aspergillus* species during the course of follow-up (Figure 3B). *Staphylococcus aureus* was recovered from sputum more frequently in NTM-positive subjects who met ATS microbiologic criteria than in NTM-positive subjects who did not meet ATS criteria and in control subjects ($p < 0.01$) (Figure 3B).

Longitudinal Decline in Lung Function

The initial analysis (Model 1) included FEV₁ data collected from the prior cross-sectional study and compared control subjects, NTM-positive subjects who did not meet ATS criteria and NTM-positive subjects who met criteria. This initial model controlled for three key variables (sex, age, and body mass index) but did

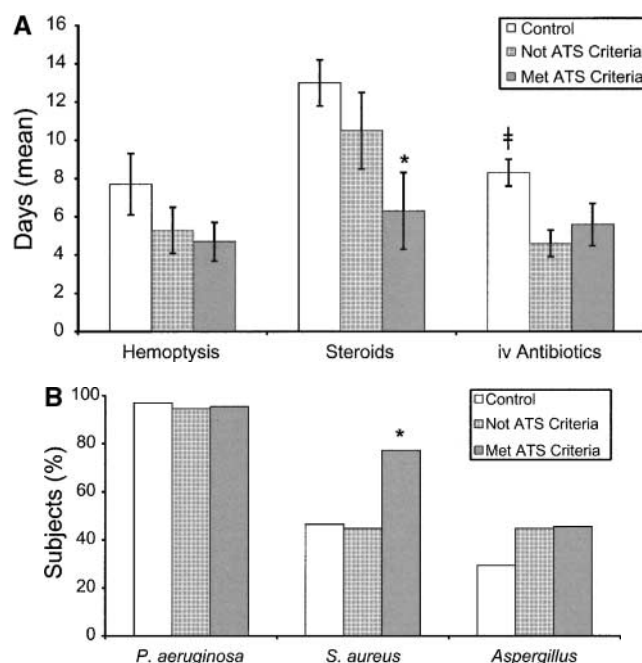


Figure 3. Potential clinical variables that may confound the relationship between NTM and decline in %FEV₁ (% predicted), plotted by groups of subjects (open bars, control subjects; hatched bars, NTM-positive subjects who did not meet ATS criteria; solid bars, NTM-positive subjects who met ATS microbiologic criteria for disease). (A) Presence of hemoptysis and use of systemic steroids and parenteral antibiotics (* $p < 0.05$, less than culture-negative control subjects. * $p < 0.05$, greater than NTM-positive subjects). (B) Sputum microbiology (* $p < 0.02$, greater than culture-negative control subjects and NTM-positive subjects who did not meet ATS criteria).

not control for differences in baseline FEV₁. The decline in FEV₁ was modest but significantly different from zero for all three groups. However, there was no significant difference in the mean annual decline in FEV₁ (% predicted) among the three groups ($1.9 \pm 0.4\%$, $1.2 \pm 0.6\%$, and $2.4 \pm 0.7\%$, respectively). The second analysis (Model 2) controlled for differences in baseline FEV₁ and the use of parenteral antibiotics and systemic corticosteroids, in addition to the variables controlled for in the initial analysis. Again, there was no significant difference among the groups ($3.2 \pm 1.1\%$, $3.1 \pm 1.8\%$, and $4.7 \pm 2.4\%$, respectively) (Figure 4).

Radiologic Assessment

Baseline and follow-up chest radiographs were available for analysis on 53 (54%) of the control subjects, 26 (68%) of the non-ATS criteria NTM-positive subjects, and 10 (45%) of the ATS criteria NTM-positive subjects. There was no significant change over time in any of the chest radiograph scores (individual category and composite) within either control subjects or the two groups of NTM-positive subjects or between the two culture-positive groups.

Entry HRCTs were available for analysis on 53 (88%) of the NTM-positive subjects and 21 (21%) of the control (NTM-negative) subjects; exit CTs were available on 24 and 8 of these two groups, respectively. Overall, the four characteristic findings associated with NTM disease were more prevalent among the NTM-positive subjects who met ATS criteria than NTM-positive subjects who did not meet ATS criteria and in the control subjects (Figure 5). Two or more of these HRCT findings were

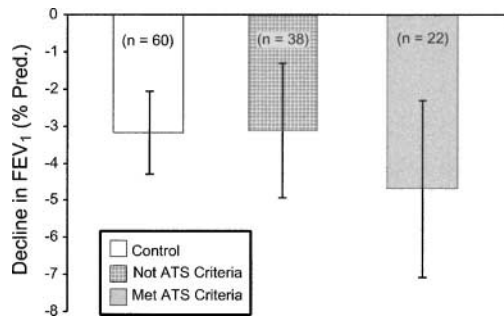


Figure 4. Annual decline in FEV₁ (% predicted) based on mixed model analyses, which shows control subjects (open bars), NTM-positive subjects who did not meet ATS microbiologic criteria (hatched bars), and NTM-positive subjects who met ATS criteria (solid bars). This analysis (Model 2) incorporated only FEV₁ data collected after the entry visit into this current study, controlled for differences in baseline FEV₁, and the use of systemic corticosteroids and intravenous antibiotics, in addition to variables in Model 1 (see METHODS).

present at baseline (entry) in a greater fraction (60%, n = 9) of the 15 subjects with three or more positive cultures as compared with 32% of those subjects with only one or two positive cultures and 19% of NTM-negative, control subjects ($p < 0.02$). Comparable differences were noted when analyses included only subjects with MAC and *M. abscessus*. More subjects who met ATS criteria and had significant baseline CT findings, and who also had exit CTs, had progression of CT findings, as compared with the other subjects with entry and exit CTs. Progression of CT findings was noted in only 3 of 8 (38%) control subjects, and 4 of 18 (22%) non-ATS criteria NTM-positive subjects, whereas all 6 (100%) of the subjects with three or more positive cultures had progression ($p < 0.0006$).

DISCUSSION

We have previously reported a high prevalence of NTM (approximately 13%) in sputum of persons with CF lung disease. This prevalence is most striking in older subjects with relatively pre-

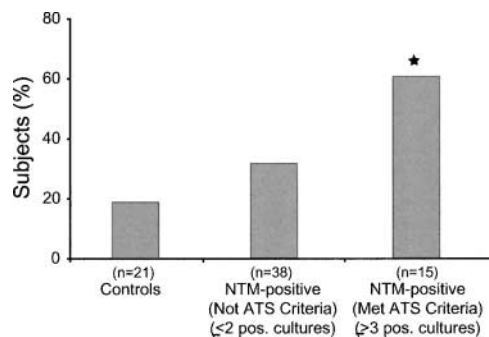


Figure 5. Characteristic HRCT findings in control subjects and NTM-positive subjects by culture status at entry (solid bars) into the study. Solid bars represent the percent of subjects in each of the three subgroups with at least two of the following characteristics on entry HRCT: (A) areas of cystic and/or cavitary parenchymal lung disease, (B) subsegmental or larger areas of parenchymal consolidation, (C) single or multiple pulmonary nodules, and (D) tree-in-bud opacities. More of the NTM positive subjects who met ATS Criteria had at least two of these findings at entry as compared with control subjects and subjects with only one or two positive cultures at entry (* $p < 0.02$).

served lung function. Anecdotal reports of these organisms coexisting in the airways of subjects with CF over prolonged periods without apparent adverse effect are interspersed with reports of precipitous declines in clinical status, which are temporally related to acquisition of NTM (3–13). The goal of this study was to assess the effect of these organisms on the short-term clinical course of CF lung disease. We identified subjects early in their acquisition of NTM and matched them to culture-negative subjects in an attempt to assess changes in lung function and chest HRCT scans more likely to be related to NTM and less likely related to some confounding variable. At entry into this cohort study these subjects remained well matched, except for a slightly lower %FEV₁ in the control subjects (Table 1).

To better assess the effect of NTM on the clinical course of CF, we grouped the NTM-positive subjects according to the ATS microbiologic criteria for disease. As reported in the previous prevalence study (1), the majority of the NTM-positive subjects had only one positive culture or two positive cultures without smear positivity, and thus did not meet the ATS microbiologic criteria for disease. Subjects from whom *M. abscessus* was cultured tended to meet microbiologic criteria more frequently than did those with only MAC or other NTM (Figure 2). Subjects who met the microbiologic criteria for NTM were not sicker than either those subjects not meeting criteria or those who remained culture-negative (controls), as assessed by frequency of hemoptysis, corticosteroid use, intravenous antibiotic use, or prevalence of *P. aeruginosa* (Figure 3A). Although patients with mycobacteria tended to have a higher reported prevalence of *Aspergillus* than did culture-negative control subjects, there was no difference in *Aspergillus* prevalence based on ATS microbiologic criteria. As reported in the previous prevalence study, a strikingly higher prevalence of *S. aureus* was seen in those NTM-positive patients who met ATS criteria as compared with NTM-positive subjects who did not meet ATS criteria and control subjects ($p = 0.02$) (Figure 3B).

We tested for change (decline) in FEV₁ over time to assess the potential effect of NTM on the course of CF lung disease. Different models were constructed to control for both key clinical variables and potential confounders. Although NTM-positive subjects who met ATS criteria tended to decline faster than both the non-ATS-positive and control subjects, the amount of variability in the slope estimates was large, and no statistically significant differences in the slopes was detected. The rate of decline in FEV₁ in the CF control subjects was similar to what has been noted in other studies of similar age patients with CF (1–3% per year) (24). There are examples in the literature suggesting a probable adverse effect of NTM on lung function. Some of those indicate a precipitous decline temporally related to recovery of NTM (4, 6, 7), whereas others note a prolonged time span between initial recovery and subsequent adverse effects (9, 12). Perhaps more significant differences in FEV₁ would be seen with a longer duration of follow-up. For example, we estimated that significant differences would be seen between NTM-positive subjects who met ATS criteria versus control subjects if the slopes declined (Figure 4) at similar rates for 6.4 years.

Given the many factors that can affect the change in FEV₁ over relatively short periods of time in patients with CF, airflow mechanics may not be the most sensitive or specific indicator of disease progression related to a specific microorganism, such as the NTM. Several studies have suggestive characteristic findings on HRCT scan in patients with NTM and without CF (20–22). More recent studies have also demonstrated progression of these findings over relatively short periods of time; one study noted progression at a mean follow-up of 28 ± 4 months and another at 28 ± 13 (range 12–42) months (25, 26). The characteristic

HRCT findings associated with NTM include cysts or cavities, segmental consolidation, peripheral nodules, and tree-in-bud type infiltrates. Although these radiographic findings may overlap with those commonly seen in CF, the relative frequency of these findings was higher in patients with CF who met ATS microbiologic criteria for NTM disease, even though their FEV₁ values were similar to those of subjects with only one or two positive NTM cultures and culture-negative control subjects. Moreover, all six of the NTM-positive subjects who had three or more positive NTM cultures as well as both entry and exit HRCT scans had progression of at least one of the four HRCT findings. In contrast, only 4 subjects out of 18 with only one or two positive cultures had these HRCT changes. This suggests that HRCT may play a vital role in the evaluation of subjects with CF and with positive NTM sputum cultures and may be an earlier indicator than FEV₁ of pathogenic infection with NTM; however, additional study will be required for confirmation.

The study was limited by sample size and length of follow-up. Sample size calculations were based on comparison of rate of change in FEV₁ for all NTM-positive subjects versus their matched culture-negative control subjects. Given the sampling variability in recovering NTM coupled with the significant HRCT findings on the entry scan of subjects who eventually met ATS microbiologic criteria, it is likely that some subjects entered the study after having had NTM in their airways for a period of time and thus were prevalent rather than incident positives. A relatively large number of subjects originally classified as culture-negative control subjects converted to NTM culture-positive, but it is less likely that subjects were misclassified as control subjects in the final analyses, given the large numbers of cultures obtained. Finally, both the revised ATS criteria for NTM pulmonary disease and longitudinal studies of the length of time for progression of HRCT findings in patients without CF and with nodular bronchiectatic disease were published after the initiation of this investigation (2, 25, 26). It seems unlikely that NTM would have the same impact in subjects with a single positive culture out of multiple specimens as compared with those subjects who had multiple positive cultures, and this notion was borne out in preliminary analyses. Thus, we believed it appropriate to group the NTM-positive subjects, based on the ATS microbiologic criteria for disease, to test the clinical impact of NTM.

Despite these limitations, this study is compatible with the general clinical approach that is evolving to address the presence of NTM recovered from the sputum of patients with CF (Figure 6). It should be noted that this current approach is based, in part, on the clinical experience that has been developed in the context of NTM in the respiratory tract of individuals with non-CF lung disease. Specifically, given the increasing prevalence of NTM with age (1) and case reports noting the potential for these organisms to cause significant clinical decline, adult patients with CF should have periodic screening cultures. During periods of clinical decline unresponsive to treatment of conventional bacterial pathogens, all patients with CF, including children, should be cultured for NTM. If a positive culture for NTM is obtained, serial specimens should be collected to assess frequency of recovery of the same species of NTM. If the ATS microbiologic criteria for NTM are met, and especially if three or more cultures are positive for the same species of NTM, a baseline HRCT scan should be obtained and assessed for the presence of (at least two of the four) characteristic findings of NTM, described previously. If the ATS microbiologic criteria are not met, periodic follow-up cultures should be obtained to look for increasing prevalence of the organisms. For *M. abscessus*, if baseline HRCT findings are suggestive of mycobacterial disease and the patient has repeated positive cultures for

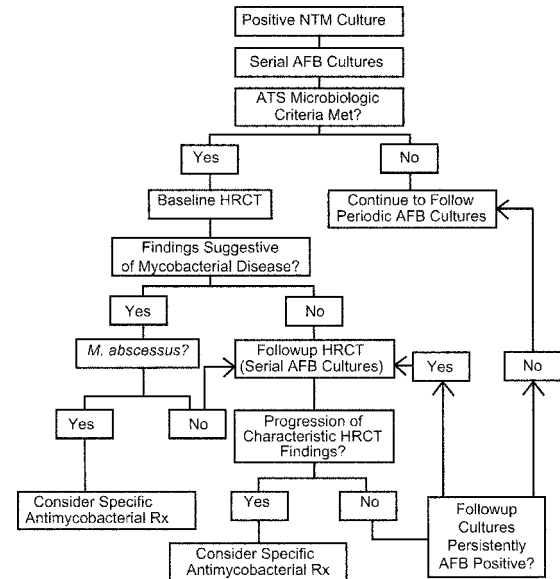


Figure 6. Flow diagram of proposed clinical approach to finding NTM in the lower airway of a patient with CF (see text for details). Further study is needed to validate this approach.

M. abscessus, consideration should be given to beginning specific antimycobacterial treatment, particularly if there is a temporally associated decline in the clinical course; this approach is based on prior reports associating this organism with significant disease in CF, (3, 5, 8, 10, 12). If the organism is not *M. abscessus*, or if characteristic HRCT findings are not present, and the patient is clinically stable, a follow-up HRCT should be obtained in 12 to 15 months, while continuing to collect serial sputum specimens for mycobacterial culture. If progression of the characteristic findings on HRCT is seen and the patient continues to have positive cultures of the same NTM organism, consideration should be given to specific antimycobacterial treatment. If HRCT progression is not noted, continued follow-up with serial HRCT scans and cultures should be performed to monitor for progression. Given the overlapping coverage of many of the drugs used to treat NTM with usual CF pathogens such as *P. aeruginosa* and *S. aureus*, airways clearance measures should be intensified, and (other) bacterial lower airway pathogens should be treated aggressively to establish a clinical baseline, before starting specific antimycobacterial treatment, so that the effect of treatment on mycobacterial disease can be better assessed.

In summary, the presence of NTM in the lower airways is common among persons with CF. The majority of persons from whom NTM are recovered will have only a single isolate with repeated cultures obtained over one to two years. On the basis of trends in lung function seen in this study, those persons from whom repeated positive cultures are obtained may be at risk of an adverse effect on lung function over a period of months to several years. Longer studies of serial lung function would be needed to confirm this. Characteristic HRCT findings of cysts or cavities, areas of consolidation, peripheral nodules, or tree-in-bud infiltrates are more prevalent in subjects with CF with repeated positive cultures, and these findings may progress over even a relatively short period of 12 to 15 months. Given the large number of confounding factors influencing the course of CF lung disease and the relative general indolent nature of these organisms, further validation of the clinical approach described previously and assessment of the effectiveness of treating these organisms in CF will require longer-term studies.

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APPENDIX

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